

WHAT IS CLAIMED IS:

1        1. An immunoglobulin molecule or fragment thereof comprising a region  
2 where amino acid residues corresponding to at least a portion of a complementarity  
3 determining region (CDR) are replaced with a peptide mimetic selected from the group  
4 consisting of an EPO mimetic and a TPO mimetic.

1        2. An immunoglobulin molecule or fragment thereof according to claim 1  
2 further comprising at least one flanking sequence including at least one amino acid  
3 covalently linked to at least one end of the peptide mimetic.

1        3. An immunoglobulin molecule or fragment thereof according to claim 2  
2 wherein the at least one flanking sequence includes a flanking sequence having a  
3 proline that is covalently linked to the peptide mimetic.

1        4. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein at least two complementarity determining regions (CDRs) are replaced with  
3 the peptide mimetic.

1        5. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the immunoglobulin molecule fragment is selected from the group consisting  
3 of Fab fragment, F(ab')<sub>2</sub> fragment and ScFv fragment.

1        6. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the immunoglobulin molecule is a full IgG molecule.

1        7. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the CDR is located on a light chain.

1        8. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the CDR is located on a heavy chain.

1        9. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the CDR is selected from the group consisting of a CDR3 of a heavy chain  
3 and a CDR2 of a light chain.

1        10. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the CDR is selected from the group consisting of CDR3 of a heavy chain and  
3 CDR2 of a heavy chain.

1        11. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the CDR is selected from the group consisting of CDR3 of a heavy chain and  
3 CDR1 of a light chain.

1        12. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein amino acid residues corresponding to a portion of more than one CDR are  
3 replaced.

1        13. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the CDR3 regions of a heavy chain and a light chain are replaced with the  
3 peptide mimetic.

1        14. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the CDR includes both CDR2 and CDR3.

1        15. An immunoglobulin molecule or fragment thereof according to claim 14  
2 wherein the CDR is located in a heavy chain.

1        16. An immunoglobulin molecule or fragment thereof according to claim 14  
2 wherein the CDR is located in a light chain.

1           17. An immunoglobulin or fragment thereof according to claim 1 wherein the  
2 EPO mimetic corresponds to the sequence set forth in SEQ. ID. NO. 3.

1           18. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the TPO mimetic corresponds to the sequence set forth in SEQ. ID. NO. 1.

1           19. An immunoglobulin molecule or fragment thereof according to claim 3  
2 wherein the CDR is replaced with a peptide having a sequence including that set forth  
3 in SEQ. ID. NO. 2.

1           20. An immunoglobulin molecule or fragment thereof according to claim 2  
2 wherein the CDR is replaced with a peptide having a sequence selected from the  
3 group consisting of SEQ. ID. NO. 25, SEQ. ID. NO. 27, SEQ. ID. NO. 29, SEQ. ID.  
4 NO. 31, SEQ. ID. NO. 33, SEQ. ID. NO. 35, SEQ. ID. NO. 37, SEQ. ID. NO. 39, SEQ.  
5 ID. NO. 41, SEQ. ID. NO. 43, SEQ. ID. NO. 45, SEQ. ID. NO. 47, and SEQ. ID. NO.  
6 49.

1           21. An immunoglobulin molecule or fragment thereof according to claim 2  
2 wherein the CDR is replaced with a peptide having a sequence selected from the  
3 group consisting of SEQ. ID. NO. 31, SEQ. ID. NO. 35, SEQ. ID. NO. 37, SEQ. ID.  
4 NO. 39, SEQ. ID. NO. 41, SEQ. ID. NO. 43, SEQ. ID. NO. 45, and SEQ. ID. NO. 49.

1           22. An immunoglobulin molecule or fragment thereof according to claim 1  
2 wherein the immunoglobulin molecule or fragment thereof is human.

1           23. An immunoglobulin molecule or fragment thereof according to claim 22  
2 wherein the immunoglobulin molecule or fragment thereof is anti-tetanus toxoid.

1           24. Nucleic acid encoding an immunoglobulin molecule or fragment thereof  
2 according to claim 1.

1        25. Nucleic acid encoding an immunoglobulin molecule or fragment thereof  
2 according to claim 2.

1        26. Nucleic acid encoding an immunoglobulin molecule or fragment thereof  
2 according to claim 21.

1        27. An expression vector comprising nucleic acid according to claim 24.

1        28. An expression vector comprising nucleic acid according to claim 25.

1        29. An expression vector comprising nucleic acid according to claim 26.

1        30. A host cell transformed with an expression vector according to claim 27.

1        31. A host cell transformed with an expression vector according to claim 28.

1        32. A host cell transformed with an expression vector according to claim 29.

1        33. A method of producing an immunoglobulin molecule or fragment thereof  
2 comprising culturing a host cell according to claim 30 under conditions suitable for  
3 expression of the immunoglobulin or fragment thereof.

1        34. A method of producing an immunoglobulin molecule or fragment thereof  
2 comprising culturing a host cell according to claim 31 under conditions suitable for  
3 expression of the immunoglobulin or fragment thereof.

1        35. A method of producing an immunoglobulin molecule or fragment thereof  
2 comprising culturing a host cell according to claim 32 under conditions suitable for  
3 expression of the immunoglobulin or fragment thereof.

1           36. A composition comprising an immunoglobulin or fragment thereof  
2 according to claim 1 and a pharmaceutically acceptable carrier.

1           37. A method of engineering an immunoglobulin molecule or fragment  
2 thereof to exhibit an activity of a biologically active peptide comprising:  
3                 providing nucleic acid encoding an immunoglobulin molecule or a  
4 fragment thereof;  
5                 replacing at least a portion of at least one CDR encoding region with  
6 nucleic acid encoding a biologically active peptide selected from the group consisting  
7 of TPO mimetic and EPO mimetic to form a biologically active peptide substituted  
8 nucleic acid construct; and  
9                 expressing the peptide encoded by the nucleic acid construct along with  
10 an antibody chain selected from the group consisting of heavy chain and light chain, in  
11 a suitable host cell such that a heterodimer is formed.

1           38. A method according to claim 37 wherein the biologically active peptide  
2 includes a proline covalently attached to its carboxy terminus.

1           39. A method according to claim 38 wherein the biologically active peptide is  
2 selected from the group consisting of SEQ. ID. NO: 31, SEQ. ID. NO: 35, SEQ. ID.  
3 NO: 37, SEQ. ID. NO: 39, SEQ. ID. NO: 41, SEQ. ID. NO: 43, SEQ. ID. NO: 45, and  
4 SEQ. ID. NO: 49.

1           40. A method of stimulating proliferation, differentiation, or growth of  
2 promegakaryocytes or megakaryocytes, comprising contacting promegakaryocytes or  
3 megakaryocytes with an effective amount of an immunoglobulin molecule or fragment  
4 thereof having one or more CDR regions replaced with a TPO mimetic peptide.

1           41. A method according to claim 40 wherein platelet production is increased.

1       42. A method according to claim 40 wherein the TPO mimetic peptide is  
2 selected from the group consisting of SEQ. ID. NO: 31, SEQ. ID. NO: 35, SEQ. ID.  
3 NO: 37, SEQ. ID. NO: 39, SEQ. ID. NO: 41, SEQ. ID. NO: 43, SEQ. ID. NO: 45, and  
4 SEQ. ID. NO: 49.

1       43. A method of increasing the production of red blood cells comprising  
2 contacting hemopoietic stem cells or progenitors thereof with an effective amount of an  
3 immunoglobulin molecule or fragment thereof having one or more CDR regions  
4 replaced with an EPO mimetic peptide.

1       44. An immunoglobulin molecule or fragment thereof comprising a region  
2 where amino acid residues corresponding to at least a portion of a CDR are replaced  
3 with a biologically active peptide flanked with a proline at the carboxy terminus of the  
4 biologically active peptide.

1       45. An immunoglobulin molecule or fragment thereof according to claim 44  
2 wherein at least two CDR regions are replaced with the biologically active peptide.

1       46. Nucleic acid encoding an immunoglobulin molecule or fragment thereof  
2 according to claim 44.

1       47. An expression vector comprising a nucleic acid according to claim 46.

1       48. A host cell transformed with an expression vector according to claim 47.

1       49. An immunoglobulin molecule or fragment thereof comprising a region  
2 where amino acid residues corresponding to at least a portion of a CDR sequence are  
3 fused to a peptide mimetic selected from the group consisting of an EPO mimetic or a  
4 TPO mimetic.

1        50. An immunoglobulin molecule or fragment thereof according to claim 49  
2 further comprising at least one flanking sequence including at least one amino acid  
3 covalently linked to at least one end of the peptide mimetic.

1        51. An immunoglobulin molecule or fragment thereof according to claim 50  
2 wherein the at least one flanking sequence includes a flanking sequence having a  
3 proline that is covalently linked to the carboxy terminus of the peptide mimetic.

1        52. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein at least two CDRs are fused to respective peptide mimetics.

1        53. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the immunoglobulin molecule fragment is selected from the group consisting  
3 of Fab fragment, F(ab')<sub>2</sub> fragment and ScFv fragment.

1        54. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the immunoglobulin molecule is a full IgG molecule.

1        55. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the CDR is located on a light chain.

1        56. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the CDR is located on a heavy chain.

1        57. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the CDR is selected from the group consisting of CDR2 of a heavy chain and  
3 CDR2 of a light chain.

1        58. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the CDR is selected from the group consisting of CDR1 of a heavy chain and  
3 CDR1 of a light chain.

102007125936000

1        59. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein amino acid residues corresponding to a portion of more than one CDR are  
3 replaced.

1        60. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the CDR is selected from the group consisting of a CDR3 of a heavy chain  
3 and a CDR3 of a light chain.

1        61. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the CDR3 regions of a heavy chain and a light chain are fused with the  
3 peptide mimetic.

1        62. An immunoglobulin molecule or fragment thereof according to claim 49  
2 wherein the CDR includes both CDR2 and CDR3.

1        63. An immunoglobulin molecule or fragment thereof according to claim 62  
2 wherein the CDR is located in a heavy chain.

1        64. An immunoglobulin molecule or fragment thereof according to claim 62  
2 wherein the CDR is located in a light chain.

1        65. Nucleic acid encoding an immunoglobulin or fragment thereof according  
2 to claim 49.

1        66. Nucleic acid encoding an immunoglobulin or fragment thereof according  
2 to claim 50.

1        67. An expression vector comprising nucleic acid according to claim 65.

1        68. An expression vector comprising nucleic acid according to claim 66.

TSD097-6059001

1        69. A host cell transformed with an expression vector according to claim 67.

1        70. A host cell transformed with an expression vector according to claim 68.

1        71. A method of producing an immunoglobulin molecule or a fragment  
2 thereof comprising culturing a host cell according to claim 69 under conditions suitable  
3 for expression of the immunoglobulin or fragment thereof.

1        72. A method of producing an immunoglobulin molecule or a fragment  
2 thereof comprising culturing a host cell according to claim 70 under conditions suitable  
3 for expression of the immunoglobulin or fragment thereof.

1        73. A composition comprising an immunoglobulin or fragment thereof  
2 according to claim 49 and a pharmaceutically acceptable carrier.

1        74. A method of engineering an immunoglobulin molecule or fragment  
2 thereof to exhibit an activity of a biologically active peptide comprising:  
3              providing nucleic acid encoding an immunoglobulin molecule or a  
4 fragment thereof;  
5              fusing at least a portion of at least one CDR encoding region with a  
6 biologically active peptide selected from the group consisting of TPO mimetic and EPO  
7 mimetic to form a biologically active peptide substituted nucleic acid construct; and  
8              expressing the peptide encoded by the nucleic acid construct along with  
9 an antibody chain selected from the group consisting of heavy chain and light chain, in  
10 a suitable host cell such that a heterodimer is formed.

1        75. A method according to claim 74 wherein the biologically active peptide  
2 includes a proline covalently attached to its carboxy terminus.

1        76. A method of stimulating proliferation, differentiation or growth of  
2 promegakaryocytes or megakaryocytes comprising contacting

3 promegakaryocytes or megakaryocytes with an effective amount of an  
4 immunoglobulin molecule or fragment thereof having one or more CDRs fused to  
5 a TPO mimetic peptide.

1 77. A method of increasing the production of red blood cells comprising  
2 contacting hemopoietic stem cells or progenitors thereof with an effective amount of an  
3 immunoglobulin molecule or fragment thereof having one or more CDR regions are  
4 fused to an EPO mimetic peptide.

1 78. An immunoglobulin molecule or fragment thereof comprising a region  
2 where amino acid residues corresponding to at least a portion of a CDR are fused with  
3 a biologically active peptide flanked with a proline at the carboxy terminus of the  
4 biologically active peptide.

1 79. An immunoglobulin molecule or fragment thereof according to claim 78  
2 wherein at least two CDR regions are replaced with the biologically active peptide.

1 80. Nucleic acid encoding an immunoglobulin molecule or fragment thereof  
2 according to claim 78.

1 81. An expression vector comprising a nucleic acid according to claim 80.

1 82. A host cell transformed with an expression vector according to claim 81.

1 83. A library containing varied immunoglobulin molecules or fragments  
2 thereof wherein amino acid residues corresponding to at least a portion of at least one  
3 CDR are replaced with a peptide mimetic selected from the group consisting of an  
4 EPO mimetic and a TPO mimetic, the peptide mimetic having at least one flanking  
5 sequence which has been randomized to generate immunoglobulin molecules or  
6 fragments thereof having variable amino acid sequences.

1        84. A library containing varied immunoglobulin molecules or fragments  
2 thereof wherein amino acid residues corresponding to at least a portion of at least one  
3 CDR are fused with a peptide mimetic selected from the group consisting of an EPO  
4 mimetic and a TPO mimetic, the peptide mimetic having at least one flanking  
5 sequence which has been randomized to generate immunoglobulin molecules or  
6 fragments thereof having variable amino acid sequences.

1           85. An immunoglobulin molecule or fragment thereof according to claim 44  
2   wherein the biologically active peptide is flanked at both its carboxy terminus and its  
3   amino terminus.

卷之三

1       86. An immunoglobulin molecule or fragment thereof according to claim 85  
2       wherein the biologically active peptide is flanked at its carboxy terminus with an amino  
3       acid sequence selected from the group consisting of proline-valine, proline-aspartic  
4       acid, proline-isoleucine, serine-asparagine, serine-lysine, serine-glycine, serine-  
5       arginine, leucine-histidine, leucine-glutamic acid, leucine-alanine, leucine-  
6       phenylalanine, valine-glutamine, valine-serine, valine-alanine, valine-asparagine,  
7       isoleucine-serine, isoleucine-tyrosine, asparagine-proline, asparagine-serine, asparagine-  
8       tryptophan, asparagine-valine, phenylalanine-valine, threonine-serine, methionine-  
9       alanine, arginine-serine, arginine-glycine, arginine-threonine, arginine-leucine,  
10      arginine-valine, tryptophan-arginine, tryptophan-tryptophan, alanine-arginine, aspartic  
11      acid-valine, glycine-tyrosine, glutamine-arginine, and glycine-lysine.

1        87. An immunoglobulin molecule or fragment thereof according to claim 44  
2 wherein the biologically active peptide is flanked at its carboxy terminus with an amino  
3 acid sequence selected from the group consisting of proline-valine, proline-aspartic  
4 acid, proline-isoleucine, serine-asparagine, serine-lysine, serine-glycine, serine-  
5 arginine, leucine-histidine, leucine-glutamic acid, leucine-alanine, leucine-  
6 phenylalanine, valine-glutamine, valine-serine, valine-alanine, valine-asparagine,  
7 isoleucine-serine, isoleucine-tyrosine, asparagine-proline, asparagine-serine, asparagine-  
8 tryptophan asparagine-valine phenylalanine-valine threonine-serine, methionine-

9 alanine, arginine-serine, arginine-glycine, arginine-threonine, arginine-leucine,  
10 arginine-valine, tryptophan-arginine, tryptophan-tryptophan, alanine-arginine, aspartic  
11 acid-valine, glycine-tyrosine, glutamine-arginine, and glysine-lysine.

1 88. An immunoglobulin molecule or fragment thereof according to claim 44  
2 wherein the biologically active peptide is flanked at its amino terminus with an amino  
3 acid sequence selected from the group consisting of tryptophan-leucine, valine-valine,  
4 glycine-proline, leucine-proline, leucine-tyrosine, serine-leucine, serine-isoleucine,  
5 serine-proline, threonine-methionine, threonine-tyrosine, threonine-proline, glutamine-  
6 threonine, glutamine-glutamic acid, glutamine-leucine, arginine-methionine, arginine-  
7 asparagine, arginine-threonine, arginine-glycine, arginine-serine, lysine-glutamic acid,  
8 lysine-glycine, alanine-histidine, histidine-glycine, histidine-leucine and asparagine—  
9 proline.

1 89. An immunoglobulin molecule or fragment thereof according to claim 85  
2 wherein the biologically active peptide is flanked at its amino terminus with an amino  
3 acid sequence selected from the group consisting of tryptophan-leucine, valine-valine,  
4 glycine-proline, leucine-proline, leucine-tyrosine, serine-leucine, serine-isoleucine,  
5 serine-proline, threonine-methionine, threonine-tyrosine, threonine-proline, glutamine-  
6 threonine, glutamine-glutamic acid, glutamine-leucine, arginine-methionine, arginine-  
7 asparagine, arginine-threonine, arginine-glycine, arginine-serine, lysine-glutamic acid,  
8 lysine-glycine, alanine-histidine, histidine-glycine, histidine-leucine and asparagine—  
9 proline.

1 90. An immunoglobulin molecule or fragment thereof according to claim 4  
2 wherein the at least two CDRs are selected from the group consisting of heavy chain  
3 CDR3-heavy chain CDR2, heavy chain CDR3-light chain CDR2, heavy chain CDR2-  
4 light chain CDR2, heavy chain CDR3-heavy chain CDR2-light chain CDR2 and heavy  
5 chain CDR3-light chain CDR1.

1        91. An immunoglobulin molecule or fragment thereof according to claim 4  
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.  
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.

1        92. An immunoglobulin molecule or fragment thereof according to claim 45  
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.  
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.

1        93. An immunoglobulin molecule or fragment thereof according to claim 52  
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.  
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.

1        94. A method of determining whether a substance has cMpl receptor activity  
2 comprising:  
3              co-transfected full length cMpl receptor with a c-Fos promoter luciferase  
4 reporter construct;  
5              starving the cells;  
6              stimulating the cells with the substance;  
7              harvesting the cells; and  
8              measuring luciferase activity.

1        95. A plasmid comprising SEQ ID NO. 111.  
1